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Practical Guidelines on Fluid Therapy

Dr. Sanjay Pandya

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Dr. Sanjay Pandya, Consulting Nephrologist

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INTRODUCTION

Fluid resuscitation is defined as a rapid administration of intravenous fluids used to restore or maintain a patient's circulatory volume during severe hypovolemia or shock due to significant and sudden fluid or blood losses. The most common indications of fluid resuscitation in critically ill patients are severe hypovolaemia, sepsis, trauma, burn, and perioperative volume loss [1]. The objective of fluid resuscitation is to quickly administer a large fluid volume to restore circulating volume, stabilize hemodynamics, and thereby restore tissue perfusion and oxygen delivery without causing harm due to fluid overload [2]. Identifying the cause of shock and treating it simultaneously is vital.

TIMING AND RATE OF FLUID ADMINISTRATION

Hypovolemic shock is a medical emergency, and fluid resuscitation should begin immediately. Delay in therapy can lead to ischemic injury and possibly to irreversible shock and multiorgan system failure. For initial fluid resuscitation, crystalloid fluids containing 130–154 mEq/L sodium are infused as a bolus of 500 mL within 15 minutes [1, 3]. Usually, one to two liters of fluid is administered rapidly to establish hemodynamic stability, maintain adequate blood flow to organs, and improve tissue perfusion. Fluid resuscitation should be done under close monitoring in high-risk patients who have kidney impairment or congestive heart failure to avoid fluid overload.

As per Surviving Sepsis Campaign recommendations (2021), in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours [4]. The use of an average fluid volume of around 30 mL/kg was supported by the PROCESS [5], ARISE [6], and PROMISE trials [7], where patients, on average, received this volume of fluid before randomization.

As early aggressive fluid resuscitation with large-bore IV cannulas is crucial in severe sepsis and septic shock, fluid resuscitation should be initiated earliest (after obtaining blood for measuring lactate and blood cultures) and should be completed within the first 3 hours. Earlier fluid resuscitation (within the first 3 hours) improves survival in patients with severe sepsis and septic shock [4]. Delayed administration of fluid (>2 hours after diagnosis) is the most crucial predictor of the fluid refractory state, which is associated with longer hospital stays and higher mortality [8].

If the patient does not respond to adequate fluid resuscitation, consider using vasopressors and inotropes and rule out other causes of shock besides hypovolemia (e.g., cardiogenic shock, sepsis) [9]. Consider earlier use of vasopressors in patients at risk of volume overload and to achieve the initial mean arterial pressure (MAP) target more rapidly.

An initial target of fluid resuscitation is to achieve a mean arterial pressure (MAP) of 65 mmHg [4]. Following initial fluid resuscitation, additional fluid infusion is planned based on a frequent assessment of clinical parameters, hemodynamic status, and laboratory tests.

The requirement for IV fluids changes over time. During the early salvage phase of shock (0–24 h), rapid fluid replacement in an adequate volume is essential. Fluid requirements decrease subsequently during

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optimization and stabilization phases (24–96 h), so the volume of fluids infusion should be reduced. Restrictive strategy during the last de-escalation phase (>96 h) is associated with better outcomes [10, 11].

TYPE OF FLUIDS FOR RESUSCITATION

The choice of resuscitation fluid depends on the severity and etiology of hypovolemic shock. Three major categories of fluids used for resuscitation are crystalloid fluids (normal saline, Ringer's lactate, and other chloride-restrictive balanced crystalloids such as PlasmaLyte); colloids (albumin, hydroxyethyl starch (HES), dextran, and gelatine), and blood products (packed red blood cells).

THE PHYSIOLOGY OF FLUID SELECTION

Understating the basic physiology of the distribution of infused fluids helps in the selection of appropriate fluid for a given patient. When different IV fluids are infused, their distribution in various compartments of body fluids differs depending upon their composition (Table 8.1 and Figure 8.1). The ability of infused IV fluids to expand intravascular volume determines its effectiveness in raising blood pressure.

Avoiding 5% dextrose in the treatment of hypovolemic shock: 5% dextrose is typically avoided in the treatment of hypovolemic shock for several reasons:

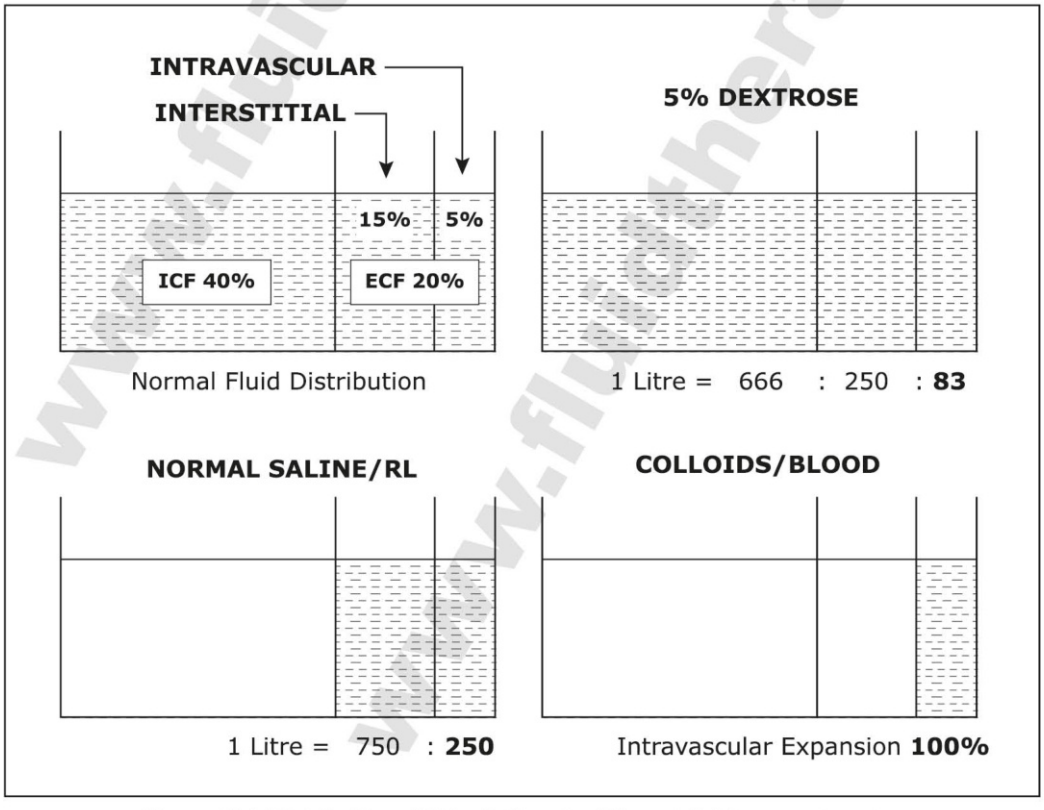

Figure 8.1 Distribution of IV solutions in different fluid compartments.

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Table 8.1 Distribution of IV solutions in body fluid compartments				
Fluid distribution (1000 ml)	**5% Dextrose**	**0.45% Saline**	**RL and 0.9% saline**	**Colloids/Blood products**
Intracellular fluid (ml)	667	333	0	0
Extracellular fluid (ml)	333	667	1000	1000
Interstitial fluid (ml)	250	500	750	0
Intravascular fluid (ml)	83	167	250	1000

1. **Poor expansion of intravascular volume:** 1000 ml of 5% dextrose increases the extracellular fluid (ECF) volume by only 330 ml, with just 83 ml (or 1/4 of the ECF) remaining in the intravascular space [12]. As 1 liter of 5% dextrose will increase the intravascular volume only by about 83 ml (8%), the rise in blood pressure will be poor in the patient with shock.
2. **Increased urine output due to osmotic diuresis:** Administering a large volume of 5% dextrose at a faster rate results in a glucose load of more than 25 gm/hour, inducing osmotic diuresis. So, even in the presence of hypovolemia, there will be increased urine output, which delays the correction of dehydration.

   Increased urine output will also create a false impression that the fluid deficit has been resolved. In such a setting, the rate of fluid replacement may be slowed down despite hypovolemia; therefore, hypotension may not improve. So, 5% dextrose should be avoided in the treatment of shock.

Selecting normal saline and Ringer's lactate as initial fluids for treating Hypovolemic shock: Crystalloid fluids such as normal saline and Ringer's lactate are sodium-rich electrolyte solutions and therefore are distributed only in the ECF compartment (25% in intravascular and 75% in interstitium). Infusion of 1 liter of these fluids will expand intravascular volume by about 250 ml, so the blood pressure rise will be much more rapid compared to 5%-dextrose [13].

As normal saline, Ringer's lactate and other chloride-restrictive balanced crystalloids are dextrose-free in an emergency when the patient's glycemic status is unknown; these fluids are safe for initial resuscitation. Moreover, compared to colloids, these fluids are inexpensive, readily available, noninfectious, reaction-free, and easy to store, so they are preferred for the initial treatment of shock.

The use of dextrose saline infusion for fluid resuscitation: Avoid using dextrose saline infusion for fluid resuscitation. 1000 ml of Dextrose saline contains 50 gm of dextrose (5% dextrose) and 154 mEq of sodium and chloride (0.9% NaCl). Faster infusion of fluid with 5% dextrose will cause hyperglycemia and resultant osmotic diuresis and increased urine output. Increased urine output in the presence of hypovolemia delays the correction of dehydration, which is not desirable. Therefore, all dextrose-containing fluids are not appropriate for fluid resuscitation [14].

Colloids and blood products: the most potent options for rapidly raising blood pressure during shock: For the prompt rise of blood pressure in shock, natural colloids (such as albumin), synthetic

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colloids (such as hydroxyethyl starches, gelatin solutions, and dextran), and blood products are more potent agents.

Large molecules of these agents do not readily cross the capillary membrane and, therefore, are primarily restricted to the intravascular compartment. In contrast to normal saline, where 3/4 of it enters the interstitium, the total volume of infused colloids and blood products remains in the vascular space. As 100% of the infused volume stays in the vascular space and selectively expands the plasma volume, they will raise blood pressure rapidly.

Colloids carry a lesser risk of pulmonary edema since the increase in plasma oncotic pressure favors fluid movements out of the interstitium into the vascular space.

Despite the physiological potency and benefits of colloids, they are not the preferred or superior solution over crystalloids in clinical practice, as discussed later.

SELECTING IV FLUID FOR RESUSCITATION

From a variety of available choices, to choose the appropriate fluid for resuscitation, consider the composition, effectiveness, benefits, and disadvantages of different solutions. Three common IV replacement fluids used to manage hypovolemic shock are crystalloids, colloids, and blood products:

- Crystalloids: The most widely used first-line therapy in managing hypovolemic shock comprises crystalloids such as normal saline, Ringer's lactate, and PlasmaLyte.
- Colloids: Colloids are second-line resuscitation therapy used in selected patients with hypotension. Among colloids, the use of natural colloids like albumin, which is safe but highly expensive, is recommended in specific clinical settings. However, the use of synthetic colloids such as hydroxyethyl starch, dextran, and gelatin is not recommended, and they are avoided or discouraged due to their harmful effects and lack of benefits.
- Blood Products: Packed red blood cells or blood substitutes are essential for effective resuscitation for patients with significant blood loss or anemia associated with hypotension.

Each type of fluid comes with its characteristics and is chosen based on the specific needs and conditions of the patient.

CRYSTALLOID RESUSCITATION: FIRSTLINE THERAPY

Crystalloids like Normal saline and balanced crystalloids like Ringer's lactate and PlasmaLyte are the most frequently prescribed crystalloid solutions for resuscitation.

The selection between normal saline and balanced crystalloids depends on their respective clinical benefits and safety profiles, not solely on physiological characteristics. This choice remains a subject of ongoing controversy. To provide a clear and comprehensive understanding of the appropriate use of crystalloids, key studies, and guidelines that provide comparative insights are summarized below:

- Composition of commonly used IV crystalloids.
- Physiological basis, advantages, disadvantages, and preferred indications for using normal saline and balanced crystalloids.
- A literature review to address the ongoing controversy between saline and balanced crystalloids.

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- Conclusions and current recommendations for appropriate use of crystalloids.

The composition of commonly used IV crystalloids

Understanding the composition of commonly used IV crystalloids is crucial for their appropriate use in resuscitation; a comparison of these compositions with human plasma is summarized in Table 8.2.

A. Normal saline

Isotonic saline, or 0.9% saline (0.9% NaCl), often referred to as "normal saline," is among the most commonly used crystalloids for resuscitation worldwide. Below are the advantages and disadvantages of using normal saline.

Advantages

Major advantages of normal saline for resuscitation include:

- **Availability and compatibility:** It is readily available, cost-effective, and compatible with the co-infusion of blood products and medications like ceftriaxone [15].
- **Volume expansion:** With 154 mEq/L of sodium, it effectively expands intravascular volume and corrects hypotension.
- **Safe for specific conditions:** It is the preferred option for patients with brain injury, hypochloremia, hypovolemic hyponatremia, and metabolic alkalosis. As the osmolarity of normal saline is 308 mOsm/L (compared to normal plasma osmolality of about 285 mOsm/kg), its use for resuscitation in neurological patients is without the risk of cerebral edema.
- **Glucose-free:** Ideal for scenarios with unknown glycemic statuses due to its lack of glucose content.

Disadvantages

The use of normal saline can be harmful, as it is neither "normal" nor "physiological" [16]. Major disadvantages of normal saline for resuscitation include:

Nonphysiological composition: Normal saline differs from the balanced crystalloid Ringer's lactate in three key aspects:

1. It has a significantly higher chloride concentration (154 versus 109 mEq/L).
2. It lacks a buffer, essential for maintaining pH.
3. It does not contain several electrolytes, like potassium and calcium, that are present in plasma.

Table 8.2 Composition of plasma and IV crystalloid resuscitation fluids

	Na^+	K^+	Cl^-	Acet.	Lact.	Ca^{2+}	Mg^{2+}	Gluc.	Osm.	SID
	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mOsm/L	mEq/L
Plasma	136–145	3.5–5.0	98–106	-	-	2.2–2.6	0.8–1.0	-	285–295	40
Normal saline	154	-	154	-	-	-	-	-	308	0
Ringer's lactate	130	4.0	109	-	28	3.0	-	-	273	28
PlasmaLyte	140	5.0	98	27	-	-	3.0	23	295	50
Sterofundin	145	4.0	127	24	-	5.0	2.0	-	309	29

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Harmful effects: Normal saline contains supraphysiologic chloride concentrations (154 mEq/L) ~50% higher than human serum chloride concentration [17]. The infusion of large volumes of this high chloride-containing fluid can lead to hyperchloremic acidosis [18, 19], an increased risk of acute kidney injury [18, 20], a greater need for renal replacement therapy, higher hospital mortality [21–23], coagulopathy [24], hyperkalemia, and more pronounced interstitial fluid retention [25].

Hyperchloremic metabolic acidosis

Infusing a large volume of normal saline often results in a normal anion gap hyperchloremic metabolic acidosis [26, 27]. This effect can be attributed to factors such as the strong ion difference (SID), reduced bicarbonate (HCO_3) reabsorption, and dilution of bicarbonate [28]:

- The SID of normal saline is zero; therefore, its infusion decreases plasma SID, leading to metabolic acidosis (SID: Normal value = 40; Normal saline = 0; RL = 28, PlasmaLyte = 50) [16, 29].
- Administering a large volume of normal saline reduces renal bicarbonate reabsorption, decreasing bicarbonate levels [30].
- Using large volumes of bicarbonate-free fluids like normal saline dilutes the bicarbonate concentration in the body, inducing dilutional acidosis [2, 31].

Risk of acute kidney injury (AKI)

Administering a large volume of normal saline can lead to hyperchloremia and an increase in chloride concentration in the distal tubular fluid. This elevated chloride level is sensed by macula densa cells located in the distal convoluted tubule. These tubular cells then transmit signals to the afferent arterioles, triggering vasoconstriction (known as "Tubuloglomerular Feedback"). This vasoconstriction, in turn, diminishes renal perfusion and reduces the glomerular filtration rate (GFR), potentially leading to acute kidney injury [16, 20, 27, 32, 33].

Use in hyperkalemia

Infusing a large volume of normal saline can induce hyperchloremic metabolic acidosis, promoting the shift of potassium out of cells and potentially causing or worsening hyperkalemia. So, the simple logic that normal saline, because it does not contain potassium, is safe to use in hyperkalemia is a myth. On the contrary, Ringer's lactate does not cause any acidosis, and in a patient with hyperkalemia, it will actually lower his serum potassium level and, therefore, is safe. Thus, Ringer's lactate is often preferred over normal saline in cases of hyperkalemia [34–36].

B. Balanced crystalloids

Emerging evidence suggests that using normal saline as a resuscitation fluid leads to complications like hyperchloremic metabolic acidosis, AKI, etc. Balanced crystalloids (buffered or chloride-restrictive solutions or balanced salt solutions) are the result of a search for safer fluid for resuscitation. Balanced crystalloids are more physiological than normal saline and are increasingly advocated as a first-line resuscitation fluid [15].

To provide a comprehensive overview of RL's optimal use, the sections below outline its basic physiology, benefits, applications in various electrolyte and clinical disorders, and potential disadvantages.

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Balanced electrolyte composition

Balanced crystalloid solutions are formulated to closely mirror the electrolyte composition, osmolality, and pH of human plasma, enabling the administration of large volumes without the risk of electrolyte disturbances.

Provides buffer to prevent or correct metabolic acidosis

Balanced crystalloids contain precursors of bicarbonate (e.g., lactate and acetate) that are metabolized into bicarbonate, helping to correct metabolic acidosis [37–39]. This buffering effect is a significant advantage over normal saline, which lacks this buffering capacity. Since bicarbonate-containing solutions are unstable in plastic containers, alternative metabolizable anions like lactate, acetate, gluconate, and malate are used to formulate balanced crystalloids to ensure stability and efficacy.

Reduces the risks of hyperchloremia

Balanced crystalloid solutions containing significantly less chloride than normal saline, effectively reduce the incidence of an increase in plasma chloride levels [40]. The potential benefit of balanced crystalloid solutions comes from their lower chloride content (<112 mEq/L) and a strong ion difference (SID) that closely matches that of human plasma. The chloride concentrations in Ringer's lactate (109 mEq/L) and PlasmaLyte A (98 mEq/L) are similar to that of human plasma (102 mEq/L), contrasting with the high chloride concentration in normal saline (154 mEq/L) [41, 42].

Effect of RL on serum lactate levels

Despite each liter of Ringer's lactate containing 28 mmol of sodium lactate, its infusion in hemodynamically stable adults only transiently elevates lactate levels or does not significantly increase them compared to normal saline solution [43–46]. As the rise in serum lactate levels is very minimal (<1.00 mmol/L) following the infusion of RL, it may not significantly interfere with the interpretation of serial lactate measurements as an index of the severity of acidosis [44, 47].

Use in lactic acidosis misconceptions and facts

Contrary to a common misconception, the infusion of Ringer's lactate does not induce lactic acidosis. The avoidance of this solution due to fears of exacerbating lactic acidosis is based on a misunderstanding.

Clarification is needed regarding the difference between lactic acid and the sodium lactate contained in Ringer's lactate. Remember that lactic acid, consisting of anion lactate plus cation hydrogen and with a pH of 2.44 to 3.51, is an "acid," and it's harmful.

However, the sodium lactate in Ringer's lactate, a "conjugate base" consisting of anion lactate and cation sodium with a pH of 6.0 to 7.3, is benign, contrasting the harmful nature of lactic acid. So, in conclusion, interestingly, RL not only has the capacity to absorb hydrogen ions, potentially correcting acidosis or leading to metabolic alkalosis, but also, importantly, it does not cause lactic acidosis [48, 49].

Safety in hyperkalemia

Ringer's lactate contains 4 mEq/L potassium, whereas the potassium content of normal saline is zero. The common apprehension that potassium-containing Ringer's lactate is unsafe and should be avoided in patients with hyperkalemia is a myth [35, 50]. As the potassium concentration of Ringer's

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lactate is just 4 mEq/L, its administration cannot raise the value of serum potassium higher than its potassium concentration (i.e., 4 mEq/L) and, therefore, cannot lead to hyperkalemia. In contrast, the low potassium content in Ringer's lactate may cause the potassium level of a hyperkalemic patient to trend toward 4 mEq/L [51, 52].

98% of potassium is distributed within the intracellular compartment, and serum potassium levels are significantly influenced by a change in pH that shifts potassium. Acidosis triggers a shift of potassium from the intracellular fluid (ICF) to the extracellular fluid (ECF). Since Ringer's lactate rectifies acidosis, it not only prevents hyperkalemia but can actually reduce serum potassium levels, supporting its safety for patients with hyperkalemia. So, we can conclude that Ringer's lactate is safer than normal saline in hyperkalemia [34, 36, 52].

Safety in neurological disorders

RL is a hypotonic fluid with a plasma osmolarity of 273 mOsm/L, lower than the normal plasma osmolality of about 285 mOsm/kg. Because of its hypotonicity, RL can cause or exacerbate cerebral edema and should, therefore, be avoided in cases with a risk of raised intracranial pressure, such as aneurysmal subarachnoid hemorrhage (aSAH), traumatic brain injury (TBI), and in patients undergoing neurosurgery [53–55].

Use in liver disorders

The lactate in RL is primarily metabolized into bicarbonate in the liver. The administration of RL is not an absolute contraindication for patients with liver dysfunction or cirrhosis, and its clinical impact remains unknown [56–58]. However, for those with severe or frank liver failure or post-liver transplantation, where a significant reduction in lactate metabolism is observed, bicarbonate-buffered solutions are often preferred over lactate-buffered ones [47, 59]. Balanced crystalloids, like PlasmaLyte, contain acetate instead of lactate, and acetate metabolism occurs in all body tissues and is not limited to liver tissues. So, PlasmaLyte can be used instead of RL in severe liver diseases.

Use in diabetic ketoacidosis

RL may be considered over normal saline for treating patients with diabetic ketoacidosis (DKA) because it is dextrose-free and reduces the risk of hyperchloremic metabolic acidosis. Additionally, it provides bicarbonate to correct acidosis and offers other benefits such as lower total cost, shorter hospital stays, and quicker, more efficient resolution of acidosis [60–63].

Precautions

Large volumes of balanced crystalloids may result in hyperlactatemia, metabolic alkalosis, and hypotonicity. As the osmolality of RL is low compared to plasma (273 vs. 290 mOsm/L), RL may exacerbate cerebral edema and therefore avoided in head injury and brain edema. As the capacity of the liver to metabolize lactate and generate bicarbonate is impaired in severe liver failure, the use of RL is avoided in such patients. Since Ringer's lactate contains calcium, it may not be suitable for co-infusion with blood products through the same IV line [15].

C. Saline vs. balanced crystalloids: A review of literature

To resolve the dilemma of choosing between normal saline and balanced crystalloids, establish the superiority

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of one fluid over the other, and provide evidence-based insights, we conducted an extensive review and analysis of various clinical trials, meta-analyses, and society guidelines. In this comprehensive review, evidence is categorized based on the superiority of each fluid, findings indicating no significant difference between the two, and insights from meta-analyses and society guidelines; a summary of conclusions and current recommendations is provided below.

1. Trials suggestive of the superiority of balanced crystalloids

- **Shaw et al. (Ann Surg 2012)** compared adult patients undergoing major open abdominal surgery who received either normal saline (30,994 patients) or a PlasmaLyte (926 patients) on the day of surgery. This study concluded that PlasmaLyte was associated with less postoperative morbidity than normal saline [64].
- **Yunus et al. (JAMA 2012)** compared the association of a chloride-restrictive vs. chloride-liberal IV fluid strategy with AKI in 760 critically ill patients. This study concluded that the chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of AKI and the use of RRT [20].
- **McCluskey et al. (Anesth Analg 2013)** compared the impact of postoperative hyperchloremia in 22,851 patients undergoing noncardiac surgery. This study concluded that postoperative hyperchloremia was associated with increased mortality, renal dysfunction, and length of hospital stay [65].
- **Raghunathan et al. (Crit Care Med 2014)** compared the outcome after resuscitation with balanced versus non-balanced fluids in 53,448 patients with sepsis in an ICU. This study concluded that among critically ill adults with sepsis, resuscitation with balanced crystalloids was associated with a lower risk of in-hospital mortality [66].
- **SMART Trial (Semler et al. NEJM 2018)** is a very large study that compared normal saline with balanced crystalloids among 15,802 critically ill adults. This study concluded that using balanced crystalloids resulted in a lower rate of death from any cause, RRT, or persistent renal dysfunction than using saline [67].
- **SALT-ED Trial (Self et al. NEJM 2018)** compared normal saline with balanced crystalloids among 13,347 noncritically ill adults. This study concluded that there was no difference in hospital-free days between both groups, but the use of balanced IV fluid resulted in a lower rate of death from any cause, RRT, or persistent renal dysfunction than the use of saline [68].

2. Trials and analysis suggestive of no difference between both groups

- **The SPLIT Trial (Young et al. JAMA 2015)** compared normal saline with PlasmaLyte in 2278 ICU patients and concluded that using a buffered crystalloid compared with saline did not reduce the risk of AKI [69]. A major limitation of this study was the median administration of a small volume of saline (<2 liters) and, therefore, a lesser risk of developing hyperchloremia.
- **The SALT Trial (Semler et al. Am J Respir Crit Care Med**

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2017) compared normal saline with balanced crystalloids in 974 ICU patients and concluded no difference in the overall incidence of AKI or major adverse kidney events [70].

- **The BaSICS Trial (Zampieri et al. JAMA 2021)**, a multicenter, double-blind RCT involving 11,000 patients, compared normal saline with balanced crystalloids and concluded that there were no significant differences in mortality rates or AKI incidence [71].
- **The PLUS Study (Finfer et al. NEJM 2022)**, a multicenter, double-blind RCT involving 5,000 patients, compared normal saline to balanced crystalloids and concluded that the balanced crystalloid group did not demonstrate reduced mortality or kidney injury [72].

3. Meta-analysis and society guidelines

- **Krajewski et al. (Br J Surg 2015)** reported in a meta-analysis of 21 studies involving 6,253 patients that the use of high-chloride fluids in perioperative or intensive care settings was associated with an increased risk of acute kidney injury, with no observed benefits on mortality [32].
- **Cochrane Database Syst Rev. (2017)** reported that perioperative administration of buffered versus non-buffered crystalloid fluids showed insufficient evidence of impacting mortality and organ system function but noted a significant reduction in postoperative hyperchloremia and metabolic acidosis with the use of buffered fluids [73].
- **Surviving sepsis campaign guidelines (Evans et al. Crit Care Med 2021):** The guidelines advise using crystalloids for both initial resuscitation and ongoing intravascular volume replenishment in adult patients with sepsis and septic shock [4]. The previous Surviving sepsis guidelines (2017) [74] suggested using either balanced crystalloids or saline, but in 2021, guidelines suggested using balanced crystalloids instead of normal saline for resuscitation [4].
- **Hammond NE et al. (NEJM Evid 2022)** conducted a Systematic Review with Meta-Analysis comparing balanced crystalloids to saline in critically ill adults and demonstrated reduced mortality in patients who received balanced crystalloids [75].
- **Beran A et al. (J Clin Med 2022)** demonstrated in their systematic review and meta-analysis that adults with sepsis treated with balanced crystalloids showed reduced mortality and AKI compared to those who received normal saline [76].
- **Isha et al. (Front Med 2023)** conducted a retrospective analysis that compared normal saline with balanced crystalloids in 2022 patients and found no significant difference in mortality rates, hospital stay, ICU admission rates, mechanical ventilation needs, oxygen therapy, and renal replacement therapy [77].

Various systematic reviews with meta-analyses and guidelines [4, 32, 73, 75, 76], except the recent one performed by Isha et al. on a small number of patients [77], suggesting that using balanced crystalloids offers some benefits compared to normal saline.

4. Trials suggestive of the superiority of normal saline

- To date, not a single study has demonstrated the superiority of saline over balanced crystalloids

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in the selection of appropriate resuscitation fluids. The absence of evidence establishing the superiority of saline indirectly reinforces the preference for using balanced crystalloids. This is consistent with the existing body of evidence highlighting the efficacy of balanced crystalloids in fluid resuscitation, even in the absence of high-quality reference evidence.

D. Crystalloids: conclusions and current recommendations

There is no clear consensus on recommending one crystalloid over others [78, 79]. However, suggestions are made based on the literature, as mentioned earlier, and various recent studies. However, it's crucial to acknowledge that the preference for using balanced crystalloids is without high-quality evidence [74, 80]. Given the low risk of harm and the real possibility of benefit, the use of balanced crystalloids could be a prudent choice in clinical practice [81]. Selecting resuscitation fluids considering history, cause, acid-base, and electrolyte disorders will be wise.

1. Balanced crystalloids preferred firstline modality

- The current trend in literature favors the use of isotonic, balanced crystalloids as preferred resuscitation fluids [67, 82–94]. The benefits of using balanced crystalloids are more evident in patients with metabolic acidosis, hyperchloremia, increased creatinine, or those at risk of kidney injury [95].
- Ringer's lactate is suggested as the preferred resuscitation fluid in sepsis [37, 42, 81], acutely ill critical patients [96–98], surgical patients [64, 99], trauma [100, 101], high risk for acute kidney injury [102], acute pancreatitis [103–105], diarrhea, burns [106] and when large volume of fluid required for resuscitation.
- Patients with acidosis should receive balanced crystalloids with an "alkalinizing" effect, while patients with alkalosis and hypochloremia should be treated with normal saline [107].
- Ringer's lactate should be avoided or used with caution in patients with severe metabolic alkalosis and hypochloremia (e.g., due to profound vomiting) [18], those with frank hepatic failure [108], and individuals with traumatic brain injury or at risk of increased intracranial pressure [18, 53].
- Although lactate metabolism may be impaired in patients with severe lactic acidosis, sepsis, or liver failure, Ringer's lactate does not cause or aggravate lactic acidosis [49, 50].
- Besides the fact that balanced crystalloids contain a small amount of potassium, the risk of hyperkalemia is significantly lower compared to normal saline [18, 35, 50].

2. Normal saline: selective use preferred

- Infusion of large quantities (>2 L) of supraphysiologic chloride containing normal saline can cause hyperchloremic metabolic acidosis, acute kidney injury [109], coagulopathy, increased hemodynamic instability, and potential mortality and therefore is harmful [110].
- Avoid administering large volumes of chloride-rich normal saline to all

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patients, especially those at high risk for AKI or incipient AKI, due to the potential risk of acute kidney injury [102, 111].

- Small to moderate amounts of normal saline do not increase the incidence of acute kidney injury [69]. Thus, modest volumes of normal saline can be administered to patients with normal kidney function in the absence of hyperchloremia and sepsis [112–114].
- Normal saline is the fluid of choice for patients with metabolic alkalosis, hypovolemia due to vomiting or upper gastrointestinal suction, traumatic brain injury, and those receiving blood products [18, 39, 87, 115–117].

SELECTION OF BALANCED CRYSTALLOID

The evidence supporting the use of balanced crystalloid solutions as preferred resuscitation fluids over saline is growing [1]. In addition to Ringer's lactate, other newer balanced crystalloids like PlasmaLyte, Sterofundin, and Ringer's acetate are commercially available. Table 8.2 provides a detailed comparison of the composition of these balanced crystalloids with the body's natural serum concentrations. However, selecting the appropriate one for practical use presents a dilemma. To choose the most suitable balanced crystalloid, considerations include:

- Understanding the difference between lactate and Acetate buffer.
- Physiological basis for limitations of Ringer's lactate.
- Understanding the composition of PlasmaLyte and its advantages.
- Evidence comparison of Ringer's lactate vs. PlasmaLyte.
- Summary and clinical indications of newer balanced crystalloids.

A. Understanding the difference between lactate and acetate buffer

Balanced crystalloids contain lactate and acetate as buffers and provide bicarbonate. Lactate is primarily metabolized in the liver, a process that can be impaired in patients with substantial liver dysfunction, extreme hypoxia, severe sepsis and septic shock, or tissue hypoperfusion due to any form of pronounced hypotension [118, 119]. In contrast, acetate is metabolized in tissues throughout the body, not just the liver, making it a more adaptable choice for patients with severe liver dysfunction [42, 120]. Importantly, metabolizing capacity of acetate is preserved in shock [39, 121]. Additionally, acetate is rapidly converted into bicarbonate and doesn't require significant oxygen, enhancing its suitability for diverse patient populations [42, 120].

B. Physiological basis for limitations of Ringer's lactate

Ringer's lactate remains the default choice among balanced crystalloids and is widely used as an effective resuscitation fluid in various clinical scenarios. However, certain compositional characteristics can make it a less suitable choice for specific patient populations. These limitations are associated with its:

- **Use of lactate as a buffer:** In cases of severe liver impairment, hypoxia, acidaemia, or shock, the body's ability to convert lactate into bicarbonate is compromised [118, 119]. This impairment leads to not only a lack of buffering benefits but also lactate accumulation

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and a rise in serum lactate levels [44]. Consequently, using lactate levels as markers for resuscitation effectiveness becomes challenging.

- **Lower osmolality:** As RL is a hypotonic fluid (osmolality of RL 278 mOsmol/L vs. plasma osmolality 290 mOsmol/L), use it with caution in neurological patients with cerebral edema [39].
- **Lower sodium content:** Since RL contains less sodium than plasma (130 mEq/L vs. 140 mEq/L serum sodium), administering it in large volumes can lead to hyponatremia.
- **Calcium content:** The presence of calcium in RL can lead to precipitation when mixed with citrate in blood transfusions [15].

C. Understanding the composition of PlasmaLyte and its advantages

The growing preference for PlasmaLyte is attributed to its unique composition, which closely mimics human plasma in terms of electrolyte content, osmolality, and pH [122]. The advantages of PlasmaLyte include not only the correction of volume and electrolyte deficits but also the improvement of acidosis. Here are the key compositional features that determine its benefits, as discussed below:

- **Use of acetate as a buffer in PlasmaLyte:** PlasmaLyte replaces the lactate in RL with anions like acetate, gluconate, and maleate as bicarbonate precursors. Acetate's ability to be metabolized both in the liver and other tissues of the body allows it to ensure the conversion to bicarbonate even in severe liver failure and shock [42, 120]. PlasmaLyte has better buffering agents and effects. Furthermore, PlasmaLyte doesn't affect serum lactate levels, ensuring accurate readings during shock.
- **Osmolality equal to plasma:** PlasmaLyte, having an osmolality equal to plasma (290 mOsmol/L), does not carry the risk of causing cerebral edema, unlike hypotonic fluids.
- **Sodium concentration similar to plasma:** The sodium concentration in PlasmaLyte is identical to that of plasma (140 mEq/L), reducing the risk of hyponatremia or hypernatremia during large-volume fluid infusion [42].
- **Free of calcium content:** Being free of calcium, PlasmaLyte mitigates the risk of calcium overload and avoids complications associated with the co-administration of blood products containing citrate, which can lead to calcium precipitation.
- **Magnesium content:** Hypomagnesemia is common in critically ill patients, and PlasmaLyte, containing 1.5 mmol/L of magnesium, can be beneficial in these cases. However, it should be used cautiously in patients at risk for hypermagnesemia.

D. A comparative review of literature on Ringer's lactate vs. acetate buffered solutions

While acetate-buffered solutions like PlasmaLyte have distinct compositional benefits, a thorough review of the existing literature is needed to determine their edge over Ringer's lactate. Recent literature offering insights into this ongoing debate is summarized below.

Evidence suggesting Acetate buffered solutions/PlasmaLyte is superior

- **Curran et al. (2021):** This systematic review with a meta-

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analysis of 24 trials noted that PlasmaLyte led to lower serum chloride and lactate levels and a higher base excess compared to Ringer's lactate, although the evidence is of low certainty [123].

- **Ellekjaer et al. (2022):** Another systematic review with a meta-analysis of five RCTs involving 390 patients found very limited, low-quality evidence supporting the use of acetate over lactate-buffered solutions in hospitalized patients for all-cause mortality [124].
- **Priyanka et al. (2023):** A study involving 80 children indicated a preference for PlasmaLyte over RL during perioperative fluid therapy for abdominal surgeries due to enhanced acid-base, serum electrolytes, and blood lactate profiles [125].
- **Abdellatif et al. (2023):** In a study with 80 children undergoing cardiac surgery, PlasmaLyte showed better lactate and calcium levels than Ringer's lactate when used as a priming solution [126].
- The inclusion of PlasmaLyte as a balanced crystalloid in recent major saline vs. balanced crystalloid trials such as SPLIT (2015), SALT (2017), SMART (2018), SALT-ED (2018), BaSICS (2021), and PLUS (2022) emphasizes its recognition and utility as a valuable option among balanced crystalloids [67–72].

Evidence suggesting equal effectiveness of Ringer's lactate and Acetate buffered solutions

- **Weinberg et al. (2018):** In a trial with 50 adults, PlasmaLyte and Hartmann's solution showed no significant differences in plasma bicarbonate levels, complications, or length of ICU and hospital stays during elective cardiac surgery with CPB [127].
- **Pfortmueller et al. (2019):** In a study of seventy-five patients undergoing cardiac surgery, the use of RL and Ringer's acetate showed similar effects on hemodynamic stability and the progression of acid-base parameters [128].
- **Rawat et al. (2020):** A study of fifty adult ICU patients with metabolic acidosis revealed no significant advantage of acetate solution over RL in either the speed or extent of acidosis correction [129].
- **Chaussard et al. (2020):** A comparison involving twenty-eight burn patients showed similar alkalinizing effects between PlasmaLyte and Ringer's lactate during fluid resuscitation. However, using PlasmaLyte resulted in significantly lower ionized calcium levels [130].

E. Summary and clinical indications of newer balanced crystalloids

The studies comparing different lactate vs. acetate-based balanced crystalloids are limited and often involve small patient cohorts, leading to no consensus on the preference for a single balanced solution [87, 131, 132]. Amongst balanced solutions, Ringer's lactate is the most preferred fluid as it is inexpensive, readily available, and its composition is favorable and more physiological. In contrast, an acetate-buffered crystalloid solution like PlasmaLyte is known for its distinct compositional advantages and is an excellent choice in specific scenarios where RL is relatively contraindicated [47]. However, it is essential to note that

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this preference has not yet escalated to the level of a strong recommendation. The trend to use newer balanced solutions like PlasmaLyte is growing, especially among critically ill patients with multiple organ failure and shock; however, their higher cost can be a limiting factor. The common conditions where the use of PlasmaLyte is suggested are outlined below:

- **Diabetic ketoacidosis:** The use of dextrose-free PlasmaLyte reduces the risk of hyperchloremic metabolic acidosis, corrects acidosis by providing bicarbonate, and offers benefits like early and faster acidosis resolution, and reduces ICU and hospital stays leading to decreased total cost [61, 133, 134].
- **Perioperative fluid therapy:** The use of PlasmaLyte may result in improved acid-base status, serum electrolytes, and blood lactate profiles [125]. It may be useful in major open GI and liver surgeries, including liver transplantation and complex cardiac surgeries [42, 135]. In postoperative patients, using PlasmaLyte for fluid replacement on the day of major surgery has been linked to lower mortality than normal saline [64].
- **Critically ill patients:** PlasmaLyte is likely the optimal choice for fluid resuscitation in most critically ill, trauma patients, except those with traumatic brain injury [136–138].
- **Priming the CPB circuit:** Using PlasmaLyte for priming in cardiopulmonary bypass can be associated with reduced metabolic acidosis and improved calcium levels [126, 139].
- **Deceased donor kidney transplantation:** Utilizing PlasmaLyte may reduce the incidence of delayed graft function in deceased donor kidney transplantation [140].

COLLOIDS: SECOND-LINE THERAPY FOR SELECTIVE USE

Colloids are potent resuscitation agents that rapidly improve hemodynamics with small volumes for longer periods. However, they are recommended for fluid resuscitation in only a select few patients and not as a routine practice. Commercially available colloids include natural colloids, such as albumin, and synthetic colloids, such as hydroxyethyl starch, dextran, and gelatin. Among these colloids, judicious use of albumin in selected patients is recommended, but synthetic colloids like hydroxyethyl starch, dextran, and gelatin are usually avoided or discouraged. The rationale for limited use or recommendation against the use of various colloids is summarized below, considering the literature on their benefits, disadvantages, and adverse effects.

A. The rationale for using colloids in resuscitation

- Greater volume expansion: As colloid solutions remain in the vascular space, plasma volume expansion is greater with colloids as compared to crystalloids [141, 142]. As the volume of colloids required to correct hypovolemic shock is less [143, 144], colloids prevent complications associated with the large volume of crystalloids, such as hyperchloremic acidosis, dilutional coagulopathy, and tissue edema. Accumulation of crystalloids in tissues, including lungs and incision sites, can cause weight gain, anasarca, and delayed tissue healing [145, 146].

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- Faster volume expansion: Colloids are statistically more effective than crystalloids in reaching resuscitative hemodynamic endpoints [147]. The benefit of speedier achievement of hemodynamic goals with colloids compared to crystalloids is less organ damage and a decreased incidence of organ failure [142].
- More prolonged volume expansion: Because of longer intravascular half-life, colloids remain in circulation for a longer period, resulting in lesser volume requirement and better hemodynamic stability compared to crystalloids [148–150].

Review of literature

Theoretical advantages of larger and rapid intravascular volume expansion with colloids are not translated to improvement in safety and long-term outcomes in several large studies and randomized controlled trials. Summaries of significant trials, systematic reviews, meta-analyses, and guidelines comparing crystalloids with colloids are provided below.

Albumin trials

- **Cochrane Injuries Group Albumin Reviewers (BMJ 1998):** Administration of albumin for fluid resuscitation in critically ill patients may increase mortality [151].
- **SAFE Study (Finfer et al. NEJM 2004):** In ICU, using 4% albumin or saline for fluid resuscitation results in similar outcomes at 28 days [152].
- **ALBIOS Trial (Caironi et al. NEJM 2014):** Comparing 20% albumin to crystalloid in 1800 septic patient resuscitation. No differences in mortality at 28 or 90 days [153].

Hydroxyethyl starch trials

- **6S Trial (Perner et al. NEJM 2012):** Increased incidence of renal replacement therapy after HES and significantly higher 90-day mortality [154].
- **CHEST Trial (Myburgh et al. NEJM 2012):** Increased incidence of renal replacement therapy after HES [155].
- **Cochrane Database Syst Rev 2013:** The review highlighted an overall increased risk of AKI and RRT in individuals treated with HES, indicating the detrimental effects of HES on kidney function compared to alternative fluids [156].
- **Recommendation of European Medicines Agency (PRCA 2013):** HES should be used at the lowest effective dose for the shortest period. HES should not be used for more than 24 hours and monitor patients' kidney function for 90 days. HES should no longer be used in patients with sepsis, burns, or critically ill patients. HES should only be used to treat hypovolaemia caused by acute blood loss when crystalloids alone are insufficient [157].
- **Recommendation of European Medicines Agency (PRCA July 2018):** Because of potential adverse effects, HES should be used with additional measures of protection in selected patients with acute blood loss, where for resuscitation, 'crystalloids' alone are not sufficient. HES should be used at the lowest effective dose for the shortest duration (dose less than 30 mL/kg and maximum duration <24 hours) for the initial phase of volume resuscitation [158].

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- **Recommendation of European Medicines Agency (July 2022):** The PRAC noted the persistent use of HES solutions in contraindicated populations, increasing the risk of severe harm and mortality. Given that the associated risks outweigh the benefits, they suspended the marketing of HES and recommended opting for safer therapeutic alternatives in line with clinical guidelines [159].

Colloids vs. crystalloids: Trials and reviews

- **CRISTAL Trial (Annane et al. JAMA 2013):** No significant difference in 28-day mortality but lower 90-day mortality in patients receiving colloids [144].
- **Cochrane Database Review of 78 RCTs (2013):** Colloids are not associated with an improvement in survival and are much more expensive than crystalloids. Because of the lack of survival benefits and higher costs, the routine use of colloids in clinical practice cannot be justified [160].
- **Cochrane Database Review (2018):** Using colloids versus crystalloids probably makes little or no difference to mortality. Starches probably slightly increase the need for blood transfusion and RRT. With the use of albumin or FFP, there is little or no difference in the need for renal replacement therapy [161].
- **A systematic review and meta-analysis (Martin et al. 2019):** A recent meta-analysis of 55 randomized clinical trials by Martin and Bassett concluded that crystalloids were less effective than colloids in stabilizing resuscitation endpoints in patients with a critical illness (e.g., shock, trauma, and sepsis) [147].
- **Surviving sepsis campaign guidelines (Evans et al. Crit Care Med 2021):** The guidelines advise using crystalloids for both initial resuscitation and ongoing intravascular volume replenishment in adult patients with sepsis and septic shock [4].

B. Colloids: Current recommendations

Based on the physiological basis, literature discussed above, and other recent reviews, various colloids' current roles, advantages, and disadvantages in fluid resuscitation are summarized below.

Colloids are potent but not safe or preferred over crystalloids

- Crystalloids and colloids are both effective, but evidence of comparative superiority and significant benefits of colloids are lacking; therefore, current trends and recommendations favor crystalloids over colloids for the resuscitation of nonseptic and septic patients [82, 83, 94, 100, 161–163], and no indications currently exist for the routine use of colloids over crystalloids [150].
- The potential benefit of colloids to provide better hemodynamic stability is due to their effectiveness in achieving greater, rapid, and prolonged intravascular volume expansion [164].
- During resuscitation, colloids are usually used along with crystalloids when patients are likely to require a large volume of crystalloids to expand the intravascular volume [165]. Adding colloids can achieve hemodynamic stability with a smaller fluid volume, thereby reducing the

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risk of positive fluid balance and the associated complications, such as fatal pulmonary edema and systemic organ dysfunction, that can arise from administering larger volumes of crystalloids [147].

- Colloid solutions other than albumin (e.g., Hydroxyethyl starch dextran, gelatin) are not used routinely because of lack of benefits, safety, and potential adverse effects. Several studies have demonstrated increased risks, including tubular necrosis and acute kidney injury (AKI), associated with synthetic colloid treatment [166].

Albumin: Safe, potent but costly option, use selectively

- Crystalloids are chosen as the first-line fluid for resuscitation for nonseptic and septic patients, and albumin should be considered a second-line agent for fluid resuscitation [4]. Albumin is used as an adjunct to crystalloids when a patient is unresponsive to crystalloids, requires substantial amounts of crystalloids to achieve hemodynamic endpoints, or cannot tolerate large-volume crystalloid resuscitation [4, 87, 147, 167]. Albumin helps to reduce the total infused volume of crystalloids for hemodynamic stability [4, 131, 168]. IV human albumin solution is more effective for resuscitation when patients have hypoalbuminemia [168]. In septic patients, early administration of the combination of albumin (particularly 20% albumin) with balanced crystalloids within the first 24 hours of treatment decreases mortality [92, 169–171]. The use of albumin is recommended in treatment of spontaneous bacterial peritonitis, hepatorenal syndrome, and large-volume paracentesis (>5 L).
- The 30 to 100 times higher cost of albumin compared to crystalloids, along with occasional supply shortages, serves as a significant limiting factor for its use [150, 172–174].
- Avoid albumin for resuscitation in patients with severe traumatic brain injury (TBI) [54, 55, 175–177]. The most likely mechanism of increased mortality in patients with severe TBI is the increased intracranial pressure associated with using albumin for resuscitation. 4% albumin is hypotonic (260 mOsmol/kg) and therefore increases brain edema [115].

Hydroxyethyl starch is harmful; avoid it

- Hydroxyethyl starch (HES) was once the most commonly used colloid, but due to its adverse effects, current recommendations are against its use [178]. HES is currently indicated as an adjuvant therapy for treating hypovolemia induced by acute blood loss when crystalloids alone are insufficient [179].
- HES is associated with several adverse effects including an increased risk of acute kidney injury, a higher need for renal replacement therapy, excessive postoperative bleeding, an increased need for blood transfusions, and a higher mortality rate [154].
- **Strict limitations and cautious use of HES:** Both the US Food and Drug Administration (FDA) [180] and the European Medicines Agency (EMA) have raised concerns about the safety of HES due to its significant harmful effects. Responding to these concerns, the EMA issued guidelines in 2013

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restricting the use of HES, and these guidelines were further tightened in July 2018 [158]. According to the revised guidelines, HES should only be administered during the initial phase of fluid resuscitation, and its dosage should not exceed 30 mL/kg. Additionally, the treatment duration should be as short as possible, not extending beyond 24 hours, and it is mandatory to monitor the patient's kidney function for at least 90 days following the administration of HES [158].

- **Advise against using HES:** Despite implementing risk minimization measures in 2018, the use of HES persisted in populations where it posed significant health risks, including an increased mortality rate. Owing to non-compliance with product guidelines and its misuse beyond approved recommendations, the EMA suspended the use of HES on 24 June 2022 [181].

Dextrans and gelatins are not recommended

- Gelatin use is associated with an increased risk of anaphylaxis, AKI, bleeding, and mortality [164, 182–184]. Given that the side effects outweigh the potential benefits [79], the Surviving Sepsis Campaign Guidelines (2021) advise against using gelatin for acute resuscitation in adults with sepsis and septic shock [4].
- Dextrans are frequently utilized in vascular surgery due to their beneficial effects, such as reducing blood viscosity and potentially enhancing microvascular circulation, particularly following grafting procedures [87]. However, their use is restricted due to associated adverse effects like antithrombotic actions [185], renal dysfunction [186], hypersensitivity reactions [187], and interference with blood grouping and cross-matching. Notably, dextrans present a higher risk of severe anaphylactic reactions compared to gelatines or starches [141].

GUIDELINES FOR BLOOD TRANSFUSION IN HYPOVOLEMIC SHOCK

In the management of hypovolemic shock resulting from massive blood loss or active bleeding, administering blood transfusions in addition to fluid replacement and hemorrhage control is essential for restoring hemodynamic stability.

Transfusion decisions should always be based on the patient's clinical state:

1. In hospitalized, hemodynamically stable adult patients, blood transfusion is necessary if the hemoglobin level drops to ≤7 gm/dL (hematocrit ≤21%) [188].
2. In patients at high risk of adverse effects, including those undergoing cardiac surgery or exhibiting evidence of myocardial or other organ ischemia, a blood transfusion is required if hemoglobin drops to ≤8 gm/dL, aiming to maintain the hemoglobin level at ≥8 gm/dL.
3. In patients with ongoing significant bleeding and hypovolemia, the need for transfusion is determined based on pulse and blood pressure, the rate of bleeding, and estimated blood loss rather than solely relying on serial hemoglobin measurements. When a large volume of blood is needed, infuse one unit of plasma, one unit of platelets, and one unit of red blood cells (1:1:1 ratio), as

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suggested by the massive transfusion protocol [189].

4. Avoid liberal blood transfusion; hemoglobin and hematocrit should not be raised over 10 gm/dL and 30%, respectively [190]. A higher hematocrit level is unnecessary for oxygen transport and may increase blood viscosity, leading to stasis in the already impaired capillary circulation.

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